

Claims 23-35 are presently pending in the instant application, with claims 28, 30, 32, and 34 under consideration by the Examiner. Applicant respectfully requests reconsideration of the claimed invention.

35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claims 28, 30, 32, and 34 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant disagrees with the Examiner's contention that the term "ligand analogue" is indefinite because it is allegedly a relative term, and also with the contention that it is allegedly unclear how to determine the requisite degree of "analogy."

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added). See also, MPEP § 2173.02 (An examiner "should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness.") (emphasis in original).

First, the phrase "ligand analogue" is not a relative term. As stated in Applicant's previous response, the phrase "ligand analogue" is commonly used by the ordinarily skilled artisan to refer to molecules that are capable of binding to a binding partner for a target ligand, but that may differ slightly in composition from the target ligand. This is, in fact, a functional expression that refers to the binding characteristics of the ligand analogue, and not a relative expression. See, MPEP § 2173.01 (an applicant is free to use functional language to make clear the boundaries of the claimed subject matter). Furthermore, this definition is fully consistent with

the use of the phrase in the claims, which refer to a ligand analogue as competing with a target ligand for binding to a ligand receptor.

In response to Applicant's argument, the Examiner states that "limitations from the specification are not read into the claims." Paper No. 12, paragraph 7. While this is certainly true, it is irrelevant to Applicant's argument, which refers to the definition of the term "ligand analogue" that is both accepted in the art and made clear in the instant application and file history. *See*, MPEP § 2173.05(a) (a patentee is free to be his or her own lexicographer, so long as that meaning is made clear in the specification or file history). Applying such a definition reads no limitations into the claims that are not present due to the use of the phrase "ligand analogue."

Moreover, the Examiner does not disagree with this definition, instead asserting that "[t]he question at hand is not what the term means but the fact that it is a relative term. *Id.* Even if the Examiner is correct in this assertion, the skilled artisan is fully informed of both the degree of analogy required to be a ligand analogue, and how to determine whether a molecule exhibits this degree of analogy. For example, the skilled artisan understands precisely how "analogous" such an analogue must be – it must be sufficiently analogous so as to bind to the target ligand's binding partner. Furthermore, the skilled artisan is fully capable of identifying such ligand analogues using simple binding assays.

Therefore, because the skilled artisan is reasonably apprised of the scope of the claims, Applicant respectfully submits that the claims meet the standard of 35 U.S.C. 112, second paragraph. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under

35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 30 and 34 under 35 U.S.C. under 35 U.S.C. 103(a) as being allegedly unpatentable over Margaron *et al.*, J. Photochem. Photobiol. B. 14: 187-199 (1992), in view of Renzoni *et al.*, U.S. Patent No. 5,135,717, and Freytag, U.S.

Patent No. 4,434,236; and claims 28 and 32 in further view of Stanton *et al.*, U.S. Patent No. 4,803,170. Applicant disagrees that the skilled artisan would have any motivation to combine the references as suggested by the Examiner.

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also*, MPEP §2143.

In the instant case, the claims relate to methods for determining the presence or amount of one or more target ligands in a sample, using a ligand analogue coupled to a signal development element comprising a water soluble hybrid phthalocyanine derivative. The hybrid phthalocyanine derivatives of the instant claims are precisely defined: at least one of the four pyrrole moieties making up the hybrid phthalocyanine derivative must be fused to a single carbocyclic ring; the other three pyrrole moieties are fused to from zero to three carbocyclic rings; and at least two of the four pyrrole moieties comprise a different number of fused rings.

In maintaining the rejection, the Examiner incorrectly asserts that “Renzoni *et al.* teach water-soluble phthalocyanine derivatives... that read directly on those of the instant claims.” Paper No. 12, paragraph 10. In fact, none of the phthalocyanine molecules disclosed in the Renzoni *et al.* patent are hybrid molecules as defined in the instant claims. Applicant believes that the Examiner intended to refer to the Margaron *et al.* publication, but respectfully requests clarification of the rejection in this regard.

The Examiner then attempts to combine the Margaron *et al.* publication with the Renzoni *et al.* patent, arguing that it would have been allegedly obvious to use the phthalocyanine derivatives disclosed by the Margaron *et al.* publication in conjugates disclosed by Renzoni *et al.*

In the previous response, Applicant noted that the Margaron *et al.* publication is related to hybrid phthalocyanine derivatives for use in cancer phototherapy, and not to the use of hybrid phthalocyanine derivatives in labeled conjugates for assay methods; and that there is nothing in the asserted *prima facie* case disclosing or suggesting that molecules useful in cancer phototherapy would be useful as labels in assay methods. In response, the Examiner first states that Applicant appears to imply that the Margaron *et al.* publication is nonanalogous art. This is incorrect. Rather, whether or not the Margaron *et al.* publication is analogous art, there still must be some motivation to combine the references in order to establish a *prima facie* case of obviousness. Because nothing of record discloses or suggests that molecules useful in cancer phototherapy would be useful as labels in assay methods, no such motivation exists.

In Paper No. 12, the Examiner asserts that one possible motivation for combining the references is that the hybrid phthalocyanine derivatives disclosed in the Margaron *et al.* publication have superior absorption properties “since this reference teaches absorption above 680 nm is preferred.” Paper No. 12, paragraph 15. There are two reasons given in the Margaron *et al.* publication for this “preference.” First, light at this wavelength is said to penetrate deeper into tissue, an “advantage” that is irrelevant to the instantly claimed methods, and which would not provide any motivation to the skilled artisan to combine the cited references. Second, the Margaron *et al.* publication states that such a wavelength makes available “less expensive and more reliable light sources” for cancer phototherapy. It is this second “advantage” on which the Examiner relies.

In arguing that “less expensive and more reliable light sources” provide some “advantage” supporting the combination of references, the Examiner states that “[i]t was well known in the art at the time of filing that absorbing toward the red end of the spectrum is advantageous because low cost semiconductor lasers can be used.” Paper No. 12, paragraph 16. Applicant respectfully requests that the Examiner provide a reference for this alleged “well known” art. *See*, MPEP § 2144.03.

The Examiner also states that the ability to use “less expensive and more reliable light sources” with dyes absorbing above 680 nm provides “a beneficial result” supporting the combination of the Margaron *et al.* publication with the Renzoni *et al.* patent. There are at least two flaws in the Examiner’s argument, however. First, any assay methods disclosed in the Renzoni *et al.* patent use “fluorescent reporting groups,” *i.e.*, phthalocyanines *See, e.g.*, Renzoni *et al.*, column 39, lines 18-26. In contrast, there is nothing of record, except Applicant’s patent application, indicating that hybrid phthalocyanine derivatives would have any fluorescent properties whatsoever. *See*, MPEP 2143 (the suggestion to combine the references must be found in the prior art, and not in applicant’s disclosure). The mere fact that the hybrid phthalocyanine derivatives disclosed in the Margaron *et al.* publication may absorb above 680 nm provides no motivation to use such molecules in the fluorescence assays disclosed in the Renzoni *et al.* patent.

Second, even if it could be argued that dyes absorbing above 680 nm provide “a beneficial result,” such dyes are already disclosed by the Renzoni *et al.* patent. *See, e.g.*, Renzoni *et al.*, column 20, lines 56-61; column 21, lines 62-67; *etc.* There is no indication in the asserted *prima facie* case as to why the skilled artisan would have any motivation to combine a reference disclosing dyes that absorb light above 680 nm, but which have unknown fluorescence properties, with a reference that already provides known fluorescent dyes capable of absorbing light above 680 nm, to provide the instantly claimed invention.

In response to Applicant’s argument that the Margaron *et al.* publication is silent as to the fluorescence properties of the disclosed phthalocyanine derivatives, the Examiner states that the Margaron *et al.* publication does disclose absorption maxima. Paper No. 12, paragraph 18. But there is nothing of record indicating that the presence of an absorption maximum is indicative of fluorescence. Applicant respectfully submits that there are numerous molecules that absorb light, but that do not fluoresce. Moreover, while it may or may not have been “well known in the art that phthalocyanine derivatives are fluorescent” (*Id.*), the Examiner has not provided any reference to support an argument that the skilled artisan would have predicted the fluorescence properties of hybrid phthalocyanine derivatives based on their fluorescence maxima.

Additionally, the Examiner also states that “the compounds of the reference meet all of the limitations of the water-soluble hybrid phthalocyanine derivatives of the claims” and that the fluorescence properties of such molecules are intrinsic in the molecule itself. *Id.* This argument ignores the fact that the Margaron *et al.* publication must be combined with additional references in order to “meet all of the limitations” of the instant method claims, and that, without some motivation to combine, a *prima facie* case of obviousness has not been established. Similarly, the fact that “the fluorescence properties of such phthalocyanine derivatives are not being claimed” (Paper No. 12, paragraph 19) does not cure the fact that the Examiner has established no motivation for the skilled artisan to combine the Margaron *et al.* publication with the Renzoni *et al.* patent.

Thus, the fact remains that there is no indication in the asserted *prima facie* case as to why the skilled artisan would consider the molecules disclosed in the Margaron *et al.* publication that are said to be useful in cancer phototherapy, to be useful as labels in fluorescence assay methods, when they have completely unknown fluorescence properties. Moreover, there is also no indication as to why the skilled artisan would be motivated to combine molecules having unknown fluorescence properties with a reference that already provides fluorescent dyes known to absorb light above 680 nm, in order to provide the instantly claimed invention.

Applicants respectfully maintain that, instead of carrying the burden of establishing a *prima facie* case of obviousness, the Examiner has fallen victim to “...decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming that it is easy to reassemble these elements into the invention...”. *In re Mahurkar*, USPQ2d 1801, 1817 (N.D. Ill. 1993). An obviousness determination cannot be premised on such an impermissible use of hindsight. *See, In re Fine*, 5 USPQ2d 1596 1600 (Fed. Cir. 1988) (“To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher.”)

Finally, Applicants also respectfully submit that, even if a *prima facie* case of obviousness has been established, the superior properties of the instant invention, in particular the advantageously large Stokes shifts of the water-soluble hybrid phthalocyanine derivatives of the instantly claimed methods, rebut that *prima facie* case. In response to Applicant's statement that the water-soluble hybrid phthalocyanine derivatives of the instantly claimed methods exhibit such advantageously large Stokes shifts and intensities, the Examiner states that no factual evidence has been provided. This, however, ignores the data provided in the instant specification, *e.g.*, in Table 2, beginning on page 85, which show that the water-soluble hybrid phthalocyanine derivatives of the instant claims exhibit Stokes shifts in excess of 100 nm (compared to the non-hybrid phthalocyanines disclosed in the Renzoni *et al.* patent, which have Stokes shifts of at most 47 nm, and more commonly less than 15 nm). These advantageously large Stokes shifts (more than double even the best dyes disclosed in the cited publications) result from the fact that the hybrid molecules appear to excite at the lowest absorbing subunit, and emit at the highest emitting subunit in the molecule, a fact which was unknown prior to Applicant's disclosure. *See, e.g.*, specification, page 33, lines 11-16.


Therefore, because there is no motivation provided to combine the references cited by the Examiner, no *prima facie* case of obviousness has been established. Furthermore, even if a *prima facie* case of obviousness has been established, the superior properties of the instant invention rebut that *prima facie* case. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,
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